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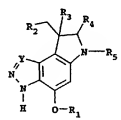
None

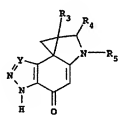
(58) Field of Search
UK CL (Edition O) **C2C CBC CKH CKR CKS CLL CTY CWC**
INT CL^6 **C07D**
ONLINE:CAS

(54) Indazole [3,2-e]-pyrrole and 1,2,3-benzotriazole [3,2-e]-pyrrole derivatives

(57) Anti-neoplastic agents of formula (I) and (II)



(I)



(II)

wherein
Y is =N- or =CR-, wherein R is hydrogen or C_1-C_4 alkyl;
R_1 is hydrogen; C_1-C_4 alkyl; -COR_6 wherein R_6 is C_1-C_4 alkyl unsubstituted or substituted by phenyl or phenyl in which the phenyl moiety or the phenyl ring is unsubstituted or substituted by 1 to 3 substituents independently chosen from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3; or -CONH-R_6 wherein R_6 is as defined above;
R_2 is halogen;
each of R_3 and R_4 independently is hydrogen or C_1-C_4 alkyl;
R_5 is hydrogen or a specified substituent; and pharmaceutically acceptable salts thereof, are provided.

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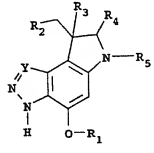
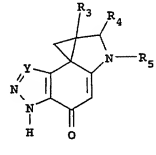
INDAZOLE[3,2-e]-PYRROLE AND 1,2,3-BENZOTRIAZOLE[3,2-e]-PYRROLE DERIVATIVES

The present invention relates to new indazole[3,2-e]-pyrrole and 1,2,3-benzotriazole[3,2-e]-pyrrole derivatives, to pharmaceutical salts thereof, to a process for their preparation, to pharmaceutical compositions containing them and to their use as therapeutic agents.

The present invention provides new compounds of formula (I) and (II)



(I)



(II)

wherein

Y is =N- or =CR-, wherein R is hydrogen or C_1-C_4 alkyl;

R_1 is hydrogen; C_1-C_4 alkyl; -COR_6 wherein R_6 is C_1-C_4 alkyl unsubstituted or substituted by phenyl or phenyl in which the phenyl moiety or the phenyl ring is unsubstituted or substituted by 1 to 3 substituents independently chosen from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3; or -$CONH$-R_6 wherein R_6 is as defined above;

R_2 is halogen;

each of R_3 and R_4 independently is hydrogen or C_1-C_4 alkyl;

R_5 is hydrogen or a substituent selected from:

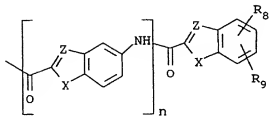
a) COR_7 in which R_7 is i) C_1-C_4 alkoxy or ii) a saturated or unsaturated, straight or branched C_1-

C_{18} aliphatic hydrocarbon chain unsubstituted or substituted by one or more substituents independently chosen from hydroxy, C_1-C_4 alkoxy, cyano, $-C(NH)-NH_2$ and $-NR'R''$ in which R' and R'', being the same or different, are hydrogen or C_1-C_4 alkyl, or iii) a saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain ω-substituted by an aryl or heteroaryl group, which in its turn is unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, hydroxy, C_1-C_4 alkoxy, cyano and $-C(NH)-NH_2$;

b) a saturated or unsaturated, straight or branched C_1-C_{18} aliphatic hydrocarbon chain unsubstituted or substituted by one or more substituents independently chosen from hydroxy, C_1-C_4 alkoxy, cyano, $-C(NH)-NH_2$ and $-NR'R''$ in which R' and R'', being the same or different, are hydrogen or C_1-C_4 alkyl;

c) a saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain ω-substituted by an aryl or heteroaryl group, which in its turn is unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, hydroxy, C_1-C_4 alkoxy, cyano and $-C(NH)-NH_2$; and

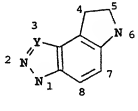
d) a group of formula (III)



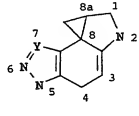
(III)

wherein n is 0, 1 or 2; each of Z group independently is -CH= or -N=; each X group independently is -O-, -S-, -NR-, wherein R is as defined above; and each of R_8 and R_9 independently is hydrogen, halogen, hydroxy, C_1-C_4 alkoxy, cyano, -C(NH)-NH_2 or -NR'R" wherein R' and R" are as defined above; and pharmaceutically acceptable salts thereof.

For clarity's sake, the following numbering is used herein for the compounds of the invention



(I)



(II)

The invention includes also all the possible isomers, typically the stereoisomers and their mixtures, the metabolites and the metabolic precursor or bio-precursors (otherwise known as pro-drugs) of compounds of formula (I) and (II).

A C_1-C_4 alkyl group is, e.g., methyl, ethyl, propyl, isopropyl and tert-butyl.

An halogen atom is preferably a bromine or chlorine.

A C_1-C_4 alkoxy group is, for example, methoxy, ethoxy, propoxy, butoxy and isobutoxy.

A saturated or unsaturated, straight or branched C_1-C_{18} aliphatic hydrocarbon chain is preferably a C_1-C_{10} alkyl, a C_2-C_6 alkenyl or a C_2-C_6 alkynyl chain, typically a C_1-C_6 alkyl chain, e.g. methyl, ethyl, propyl, isopropyl, butyl or tert-butyl, or a vinyl, propenyl, 1-, 2- or 3-butenyl, ethynyl, 1- or 2-propynyl group.

When said C_1-C_{18} aliphatic hydrocarbon chain is substituted, it is preferably substituted by 1 to 4 substituents, typically from 1 to 2 selected independently from those mentioned above.

A saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain is preferably a C_1-C_6 alkyl, a C_2-C_6 alkenyl or a C_2-C_6 alkynyl chain, typically a methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, vinyl, propenyl, 1-, 2- or 3-butenyl, ethynyl, 1- or 2-propynyl group.

An aryl group, as a substituent on said C_1-C_{12} aliphatic hydrocarbon chain is, for instance, phenyl or naphthyl, preferably phenyl.

A heteroaryl group, as a substituent on said C_1-C_{12} aliphatic hydrocarbon chain is, for instance, pentatomic or hexatomic heterocyclic ring containing from 1 to 3 heteroatoms chosen independently from nitrogen, sulphur and oxygen, or a corresponding benzoderivative thereof.

A pentatomic heterocycle ring is for example a thienyl, furyl, pyrrolyl, imidazolyl or pyrazolyl ring and a corresponding benzoderivative is, e.g., a benzofuranyl, indolyl, indazolyl or benzymidazolyl ring.

An hexatomic heterocycle ring is for example a pyridyl and a corresponding benzoderivative is, e.g., a quinolinyl ring.

According to the definition of Z and X given above, it is evident that, when n is 1 or 2, the benzoheterocyclic units contained in a group formula (III) can be either the same or different.

The single benzoheterocyclic unit contained in a group of formula (III) may be for instance a benzofuran, indole, benzothiophen, benzoimidazole, benzothiazole, benzoxazole ring and preferably a benzofuran or indole ring.

Pharmaceutically acceptable salts of the compounds of the invention include acid addition salts, with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric and phosphoric acids, or organic, e.g. acetic, propionic,

gycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic acids.

As stated above, the present invention also includes within its scope pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above, but which nevertheless upon administration to human being are converted directly or indirectly in-vivo into a compound of formula (I).

Preferred compounds of the invention are compounds of formula (I) and (II) wherein:

R_1 is hydrogen; $-COR_6$; or $-CONH-R_6$ wherein R_6 is as defined above;

R_3 and R_4 are hydrogen;

R_5 is a group of formula (III) as defined above;

R_2 and Y are as defined above and the pharmaceutically acceptable salts thereof.

More preferred compounds of the invention are compounds of formula (I) and (II) wherein:

Y is $=CH-$ or $=\overset{|}{C}-CH_3$;

R_1 is hydrogen or $-CONHR_6$ wherein R_6 is as defined above;

R2 is as defined above;

R3 and R4 are hydrogen;

R_5 is a group of formula (III) as defined above wherein Z is CH and X is independently O, NH or NCH_3; R_8 is hydrogen and R_9 is as defined above; and the pharmaceutically acceptable salts thereof.

Examples of specific preferred compounds of the invention are the following:

1) 7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

2) 1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

3) 2-(tert-butyloxycarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
4) 2-(tert-butyloxycarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
5) 2-(5-amino-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
6) 2-(5-amino-1H-indol-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
7) 2-(1H-benzofuran-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
8) 2-(1H-benzofuran-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
9) 2-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
10) 2-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
11) 2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
12) 2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
13) 2-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
14) 2-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
15) 2-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
16) 2-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

17) 2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

18) 2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

19) 2-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

20) 2-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

21) 2-[[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

22) 2-[[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydro-cyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

23) 2-[[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

24) 2-[[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

25) 3-methyl-4-(chloromethyl)-8-hydroxy-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;

26) 4-(chloromethyl)-8-hydroxy-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;

27) 3-methyl-4-(chloromethyl)-8-hydroxy-6-((tert-butyloxy)carbonyl)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;

28) 4-(chloromethyl)-8-hydroxy-6-((tert-butyloxy)carbonyl)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;

29) 3-methyl-4-(chloromethyl)-6-((tert-butyloxy)carbonyl)-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;

30) 4-(chloromethyl)-6-((tert-butyloxy)carbonyl)-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;

31) 3-methyl-4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

32) 4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

33) 3-methyl-4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

34) 4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

35) 3-methyl-4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

36) 4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

37) 3-methyl-4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

38) 4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

39) 3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

40) 4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

41) 3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

42) 4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

43) 3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

44) 4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

45) 3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

46) 4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

47) 3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

48) 4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

49) 3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

50) 4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

51) 3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl) carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

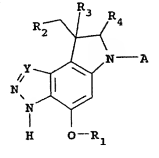
52) 4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

53) 3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl) carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

54) 4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole; either as single isomers or a mixture thereof and the pharmaceutically acceptable salts thereof.

The compounds of formula (I) and (II), according to the present invention, and the salt thereof can be obtained by a process comprising:

a) removing the protecting group in a compound of formula (IV)



(IV)

wherein A is an amino protecting group, R_1 is hydrogen and Y, R_2, R_3, R_4, are as defined above, under acidic

conditions, thus obtaining a compound of formula (I) in which R_1 and R_5 are hydrogen; or

b) reacting a compound of formula (I), wherein R_5 is hydrogen and Y, R_1, R_2, R_3 and R_4 are as defined above, with a compound of formula (V)

$$R'_5\text{-}W \qquad (V)$$

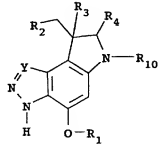
wherein R'_5 is as R_5 defined above under a) or d) and W is OH or a good leaving group, thus obtaining a compound of formula (I) wherein R_5 is as defined above under a) or d), respectively; or

c) reacting a compound of formula (I), wherein R_5 is hydrogen and Y, R_1, R_2, R_3 and R_4 are as defined above, with a compound of formula (VI)

$$R''_5\text{-}W' \qquad (VI)$$

wherein R''_5 is as R_5 defined above under b) or c) and W' is halogen, thus obtaining a compound of formula (I), wherein R_5 is as defined above under b) or c), respectively; or

d) reacting a compound of formula (VII)



(VII)

wherein R_1 is hydrogen, R_{10} is either an amino protecting group or as R_5 as defined above under a) to d) and Y, R_2, R_3 and R_4 are as defined above, with a compound of formula (VIII)

$$W'\text{-}C_1\text{-}C_4 \text{ alkyl} \qquad \text{(VIII)}$$

wherein W' is halogen, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I), wherein R_1 is C_1-C_4 alkyl; or

e) reacting a compound of formula (VII) as defined above with a compound of formula (IX)

$$W\text{-}COR_6 \qquad \text{(IX)}$$

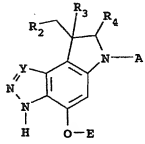
wherein W and R_6 are as defined above, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I) wherein R_1 is $-COR_6$; or

f) reacting a compound of formula (VII) as defined above with a compound of formula (X)

$$R_6\text{-}N{=}CO \qquad \text{(X)}$$

wherein R_6 is as defined above, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I) wherein R_1 is $-CONR_6$; or

g) removing the amino and hydroxy protecting groups in a compound of formula (XI)



(XI)

wherein E is a hydroxy protecting group, A is an amino protecting group and Y, R_2, R_3 and R_4 are as defined above, thus obtaining a compound of formula (I) wherein R_1 and R_5 are hydrogen; or

h) removing the hydroxy protecting group in a compound of formula (XI) wherein A, being as defined above is -COO-tert-butyl and E, Y, R_3 and R_4 are as defined above, thus obtaining a compound of formula (I) wherein R_1 is hydrogen and R_5, being a COR_7 group as defined above, is -COO-tert-butyl; or

i) reacting a compound of formula (I), in which R_1 is hydrogen and Y, R_2, R_3, R_4 and R_5 are as defined above, with a basic agent, thus obtaining a compound of formula (II);

and if desired, converting a compound of the invention into another compound of the invention, and/or, if desired converting a compound of the invention into a salt thereof, and/or, if desired converting a salt of a compound of the invention into a free compound, and/or, if desired, separating a mixture of isomers of a compound of the invention into the single isomers.

Process-variants a) to i) according to this invention are analogy processes. For instance they can be performed as described herebelow.

In a compound (IV) A as amino protecting group is for instance an amino protecting group according to the

peptidic chemistry. Preferably it is a benzyloxycarbonyl or a C_1-C_4 alkoxycarbonyl group, in particular a tert-butoxycarbonyl group.

Removal of an amino protecting group in a compound of formula (IV) can be carried out using known methods, e.g. as described in J.Org.Chem. 43, 2285 (1978).

In a compound of formula (V) W as a leaving group is for instance a halogen atom, preferably chlorine, an imidazolyl group or a C_1-C_4 alkoxy group, preferably tert-butoxy.

The reaction of a compound of formula (I) with a compound of formula (V) can be carried out according to known methods. If necessary the hydroxy group in a compound of formula (I) can be protected before the reaction takes place and then deprotected at the end of the reaction, according to known methods. Examples of hydroxy protecting groups are benzyl or tetrahydropyranyl.

The reaction between a compound of formula (I) and a compound of formula (V) wherein W is OH, is preferably carried out in a molar ratio ranging from about 1:1 to about 1:2 in an organic solvent such as, dimethylsulfoxide, dioxane, or preferably dimethylformamide in presence of a condensing agent such as, N,N'-dicyclohexylcarbodiimide or preferably 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride.

The reaction temperature may vary from about -10° to about 60° C and the reaction time from about 1 to about 24 hours.

The reaction between a compound of formula (I) and a compound of formula (V) wherein W is a leaving group as defined above, may be carried out in a molar ratio ranging from about 1:1 to about 1:2 in an organic solvent such as, dimethylformamide, dioxane, or an aqueous mixture thereof in the presence of an organic base, e.g. sodium bicarbonate, at a temperature from about 0°C to about 100°C and for a time varying from about 2 to about 48 hours.

In a compound of formula (VI) W' as halogen atom is, e.g., chlorine or bromine. When reacting a compound of formula (I) with a compound of formula (VI), if necessary the

hydroxy group in the compound of formula (I) can be protected and then deprotected at the end of the reaction as described above.

The reaction of a compound of formula (I) with a compound of formula (VI) can be carried out for instance as described in J.Am.CHem.Soc. 54, 1499 (1932); ibidem 3441; ibidem 4457; ibidem 82, 6163 (1960).

In a compound of formula (VII) R_{10} as amino protecting group can be for instance an amino protecting group known from the chemistry of peptides and if desired can be removed according to known methods at the end of any reaction according to process variants d), e) and f).

In a compound of formula (VIII) W' as halogen atom is, e.g., chlorine or bromine. The reaction of compound of formula (VII) with a compound of formula (VIII) can be carried out according to known methods for instance those described above as to the reaction of a compound of formula (I) with a compound of formula (VI).

In a compound of formula (IX) W as a leaving group is for instance one of the groups mentioned above as to a compound of formula (V). The reaction of a compound of formula (VII) with a compound of formula (IX) can be carried out by following the same procedures described above as to the reaction of a compound of formula (I) and a compound of formula (V).

The reaction of a compound of formula (VII) with a compound of formula (X) can be performed according to known methods, e.g. as reported in J.Org.Chem. 42, 1428 (1977); Synthesis 131 (1989); J.Chem.Soc. Perkin Trans. 2, 1029 (1985).

A hydroxy protecting group in a compound of formula (XI), according to process-variants g) and h), can be a hydroxy protecting group known from the chemistry of peptides, e.g. one of those mentioned above. Similarly, an amino protecting group in a compound of formula (XI), according to process g), can be one of those known from the chemistry of peptides; for instance, one of those mentioned above. Selective removal of the hydroxy protecting group in a

compound of formula (XI), according to process h), can be performed by using known methods as those reported in J.Org.Chem. 44, 3442 (1979); Synthesis 76 (1985).

The same methods can be used for removing the hydroxy protecting group in a compound of formula (XI), according to process g); removal of the amino protecting group in the same compound can be carried out using known methods as, e.g., those described in J.Org.Chem. 43, 2285 (1978).

A basic agent according to process variant i) can be either an inorganic or an organic base such as an alkaline carbonate or bicarbonate salt or a trialkylamine, preferably triethylamine. The reaction can be carried out in an organic solvent such as e.g., dioxane, acetonitrile, tetrahydrofuran or their aqueous mixtures. The reaction time may vary from about 2 to about 48 hours and the reaction temperature from about 0°C to about 50°C.

The optional salification of a compound of formula (I) or (II), as well as the conversion of a salt thereof into a free compound and the separation of a mixture of isomers of a compound of formula (I) or (II) into the respective single isomers can be carried out according to known methods.

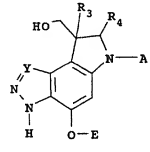
A compound of the invention, if desired, can be converted into another compound of the invention according to known methods. For instance, a compound of formula (IV) in which the amino protecting group A is tert-butoxycarbonyl can be regarded as a compound of formula (I) in which R_5 is $-COR_7$ in which R_7 is tert-butyloxy. Similarly, a compound of formula (VII) in which R_{10} is as R_5 defined under a) to d) can be regarded as a compound of formula (I) in which R_5 is as defined above under a) to d). Therefore reactions involving a compound of formula (IV) or of formula (VII) can be regarded, according to particular values of the substituents, as a conversion of a compound of formula (I) into another compound of formula (I). Similarly, processes b) and c) are acylation and alkylation reactions, respectively, on a compound of formula (I), namely

conversions of a compound of formula (I) into another compound of formula (I).

The compounds of formula (IV) are either compounds of formula (I), as stated above, or can be obtained by removing the hydroxy protecting group in a compound of formula (XI) according to known methods.

The compounds of formula (VII) are either compounds of formula (I), as stated above, or can be obtained by removing the amino protecting group in a compound of formula (XI), according to known methods, and then acylating or alkylating the free amino group as per processes b) and c), respectively, in order to introduce the R_{10} substituent, followed by removal of the hydroxy protecting group by known methods.

According to a preferred embodiment of the invention the compounds of formula (XI) may be prepared by alogenating a compound of formula (XII)



(XII)

wherein Y, A, E, R_3 and R_4 are as defined above, with an halogenating agent, e.g. carbon tetrachloride and triphenylphosphine.

The reaction can be carried out using known methods as those reported in J.Am.Chem.Soc. 111, 6461 (1989).

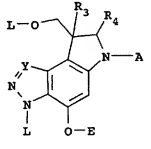
The compounds of formula (XI) are new compounds and are a further object of the present invention.

The compounds of formulae (V), (VI), (VIII), (IX) and (X) are either known compounds or can be obtained from known compounds according to known methods.

For instance the following compounds of formula (V) in which R'_5 is a group d) as defined above are known from the following literature:

1H-benzoimidazole-2-carboxylic acid [J.Chem.Soc. Perkin Trans. 1, 2871 (1982)]; 2-benzothiozolecarboxylic acid, ethyl ester [Tetr. Letters 23, 3357 (1982)]; 2-benzofuran carboxylic acid [Org.Synth.Coll. III, 209-211]; 5-amino-1H-indole-2-carboxylic acid [C.A. Reg. No. 71086-99-2]; 5-amino-1H-indole-2-carboxylic acid [J.Am.Chem.Soc. 80, 4621 (1958); 5-hydroxy-1H-indole-2-carboxylic acid [C.A. Reg. No. 21598-06-1]; 5-hydroxy-benzo[b]-thiophene-2-carboxylic acid, methylester [C.A. Reg. No. 82788-15-6].

A compound of formula (XII) may be prepared from a compound of formula (XIII)



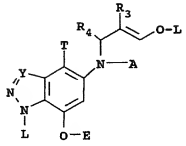
(XIII)

wherein R_3, R_4, E, Y, and A are as defined above and each L group, being the same or different, is a protecting group preferably a tethrahydropyranyl group.

The reaction can be carried out using an organic protic solvent, typically a C_1-C_3 alkanol, preferably ethanol, in the presence of catalytic amounts of p-toluenesulfonic acid.

The reaction temperature may vary from about -10°C to about 50°C and the reaction time from about 1 to about 24 hours.

A compound of formula (XIII) can be obtained by cyclizing a compound of formula (XIV)



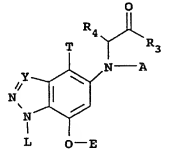
(XIV)

wherein Y, R_3, R_4, A, E and L are as defined above and T is an halogen such as chlorine, fluorine, or preferably bromine.

The reaction can be carried out in an organic solvent such as dioxane, tetrahydrofuran or preferably benzene under argon with commercial α,α'-azo-bisisobuthyronitrile and tris(trimethylsilyl)silane.

The reaction temperature may vary from about 20°C to about 100°C and the reaction time from about 1 to 5 hours.

A compound of formula (XIV) can be prepared from a compound of formula (XV)



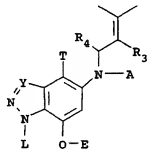
(XV)

wherein R_3, R_4, Y, A, E, L and T are as defined above with triphenyl [(2-tetrahydropyranyloxy) methyl] phosphonium chloride in an organic solvent such as tetrahydrofuran, hexane or dioxane, through a Wittig reaction.

The reaction can be carried out using phosphonium salt, about 1 eq. of n-butyllithium as base in the first step and about 0.3 eq. of compounds of formula (XV) in presence of

about 1 or about 1.2 eq. of hexamethylphosphoramide in the second step.
The reaction temperature in the two steps may vary from about -78°C to about 50°C and the reaction time from about 1 to about 48 hours.
The phosphonium salt may be prepared using known methods as those reported in Tetrahedron 31, 89 (1975).

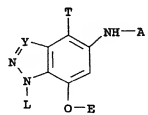
A compound of formula (XV) can be prepared by ozonolysis of a compound of formula (XVI)



(XVI)

wherein R_3, R_4, Y, A, E, L and T are as defined above.
The reaction can be carried out in a mixture of methylene chloride-pyridine with a stream of 3% O_3/O_2.
The reaction temperature may vary from about -78°C to about 0°C and the reaction time from about 5 minutes to about 12 hours.

A compound of formula (XVI) can be prepared from a compound of formula (XVII)



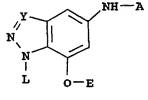
(XVII)

wherein Y, A, E, L and T are as defined above, with compounds of formula (XVIII)

(XVIII)

wherein R_3, R_4, and T are as defined above.
The reaction can be carried out in an organic solvent such as, e.g., dioxane, tetrahydrofuran or preferably dimethylformamide under argon, using about 3 eq. of allylic halogenide and about 2 eq. of sodium hydride 60% in oil.
The reaction temperature may vary from about -10°C to about 50°C and the reaction time from about 1 to about 12 hours.
The compounds of formula (XVIII) are commercial compounds or may be prepared using known methods.

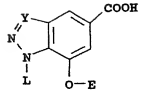
A compound of formula (XVII) can be prepared by halogenation of a compound of formula (XIX)



(XIX)

wherein Y, A, E and L are as defined above.
The reaction can be carried out according known procedure as those reported in J.Am.Chem.Soc. 80, 4327 (1958) and J.Org.Chem. 30, 304 (1965).

The compounds of formula (XIX) may be prepared from a compound of formula (XX)



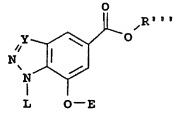
(XX)

wherein Y, E and L are as defined above.

The reaction can be carried out in an organic solvent such as an aliphatic C_1-C_4 alcohol, preferably tert-butanol, using from about 1 to about 1.5 eq. of diphenylphosphoryl azide in presence of about 1.2 eq. of an organic base such as, e.g., triethylamine.

The reaction temperature may vary from about 0°C to about 150°C and the reaction time from about 5 to about 24 hours.

A compound of formula (XX) can be prepared by hydrolysis of a compound of formula (XXI)

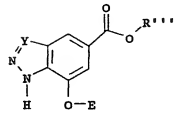


(XXI)

wherein Y, E and L are as defined above and R''' is a C_1-C_4 alkyl group, such as methyl, propyl, isopropyl or preferably ethyl.

The reaction can be carried out by hydrolytic condition according to known procedure, using for instance NaOH, KOH or preferably LiOH in a mixture of water and organic solvent such as, e.g., dioxane, tetrahydrofuran, methanol, ethanol or acetonitrile, at room temperature and for a time from about 2 to about 24 hours.

A compound of formula (XXI) can be prepared from a compound of formula (XXII)

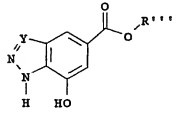


(XXII)

wherein Y, E and R''' are as defined above.

The reaction can be carried out according to known procedure [e.g. Synth.Commun. 9, 271 (1979)] using 3,4-dihydro-2H-pyrane and a catalytic amount of p-toluensulfonic acid in an organic solvent such as, e.g., dioxane, tetrahydrofuran or methylene chloride.

A compound of formula (XXII) can be prepared from a compound of formula (XXIII)

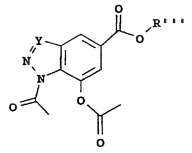


(XXIII)

wherein Y and R''' are as defined above.

The reaction can be carried out according to known procedure as those reported in Methods Carbohydr.Chem. II, 166 (1963), using benzyl bromide and K_2CO_3 in an organic solvent such as, e.g., dimethylformamide.

A compound of formula (XXIII) can be prepared from a compound of formula (XXIV)



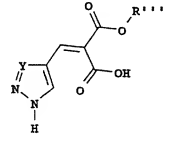
(XXIV)

wherein Y and R''' are as defined above.

The reaction can be carried out in an organic solvent such as, e.g., methanol or preferably ethanol in presence of an excess of inorganic base such as, e.g., sodium carbonate or potassium carbonate.

The reaction temperature may vary from about 70°C to about 90°C and the reaction time from about 12 to about 24 hours.

A compound of formula (XXIV) can be prepared by cyclizing a compound of formula (XXV)

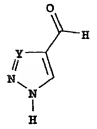


(XXV)

wherein Y and R''' are as defined above.

The reaction can be carried out in an organic solvent such as, e.g., acetic anhydride in presence of an excess of sodium acetate according to known procedure as those reported in J.Med.Chem. Vol. 31, 590 (1988).

A compound of formula (XXV) can be prepared from a compound of formula (XXVI)



(XXVI)

with diethysuccinate, using a known procedure as reported in Helv.Chim.Acta 62, 90 (1979).

The reaction can be carried out in an organic solvent such as, e.g., tert-butanol in presence of an organic base such as, e.g., potassium tert-butoxide.

The reaction temperature may vary from about 80°C to about 130°C and the reaction time from about 1 to about 12 hours.

The compounds of formula (XXVI) are known compounds or may be prepared using known methods, see for example J.Am.Chem. Soc. Vol. 71, 1436 (1949); J.Het.Chem. 7, 25 (1970).

When in the reactions involving the intermediate compounds of the present invention, free hydroxy and/or amino group need to be protected before the reaction take place and deprotected at the end of the reaction, such protections and deprotections can be carried out as known from the peptide chemistry, for instance as herein described.

PHARMACOLOGY

The compounds of the invention have cytotoxic properties toward tumor cells.

The cytotoxicity of the compounds of the invention was evaluated, for instance, on murine L1210 leukemia cells, sensitive and resistant to Doxorubicin with the following procedure.

Cells were derived from in vivo tumors and established in cell culture.

Cells were used until the tenth passage and cytotoxicity was determined by counting surviving cells after 48 hours treatment.

The compounds of the invention were found to be active also in-vivo on murine L1210 leukemia and on murine reticulosarcoma M 5076.

By virtue of their valuable properties, the compounds of the present invention, and the pharmaceutically acceptable salts thereof, can be useful in therapy as antineoplastic agents, e.g. to inhibit the growth of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors. Other neoplasias in which the compounds of the invention can find application are, for instance, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

The compounds of the invention can therefore be used in a treatment to ameliorate a cancer pathology.

The compounds of the invention can be administered to mammals, including humans, by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally.

The administration dosage of these drugs will vary depending upon the disease status of the individual.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

For example, a suitable dosage for administration to adult humans of compound 2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetra-hydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one may range from about 0.05 to about 20 mg pro-dose 1-4 times a day.

Object of this invention is also to provide a pharmaceutical composition comprising a compound of the invention, i.e. a compound of formula (I) or (II), as

defined above or a pharmaceutically acceptable salt thereof, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers. The pharmaceutical compositions are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions for intramuscular injections may contain, together with the active compound a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, polyethylene (20) sorbitan mono-oleate, and if desired, a suitable amount of lidocaine hydrochloride.

In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl-cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

Furthermore, according to the present invention there is provided a method of treating tumors in a mammal, including humans, in need of it, comprising administering to said mammal a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

The following examples illustrate but do not limit the invention.

The abbreviations DMF, THF and PMR stand, respectively, for dimethylformamide, tetrahydrofuran, and Proton Magnetic Resonance. The term "indazole" is meant herein to define the "1H-indazole" ring moiety.

Example 1

(±)-2-(tert-butyloxycarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa-[c]-pyrazo-[4,3-e]indol-4-one [compound (II), no. 3]

Step -1- **The intermediate 4-formyl-3-methyl-pyrazole**

To a stirred solution of dry DMF (6 mL), cooled at 0°C, was added dropwise 3.42 mL (37 mmol) of Thionyl chloride. At this solution was added in small portions 2 g (17 mmol) of semicarbazone.

The resulting mixture was warmed at 50-60°C for 4 hours. After this time the mixture was poured in iced water (20 mL) and 6.8 g (0.17 mol) of NaOH, dissolved in distilled water (15 mL), were added. The mixture was warmed at 50°C for 5 minutes, then cooled at room temperature and acidified to pH 6 with aqueous 20% HCl. The aqueous solution was extracted with Ethyl acetate (4x30 mL) and the recombined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography to afford the intermediate as a yellow solid (1.68 g, 90%).

m.p. (EtOAc-light petroleum) 93-94°C
IR (KBr) cm^{-1}: 3450, 1675, 1450
PMR ($CDCl_3$) δ:
2.42 (s, 3H), 8.02 (s, 1H), 9.82 (s, 1H), 13.2 (bs, 1H)

Step -2- **The intermediate E-Ethyl-4-[(3-methyl)-pyrazol-4-yl]-3-ethoxycarbonyl-3-butenoate**

A solution of Potassium tert-butylate (21 g, 0.19 mmol) in tert-Butanol (81 mL) was added to a mixture of 4-formyl-3-methyl-pyrazole (6.93 g, 63 mmol) and diethyl succinate (40.2 mL, 0.285 mmol) and refluxed for 45 minutes. Then the same amounts of diethyl succinate and Potassium tert-butylate in tert-Butanol were added and the mixture refluxed for other 45 minutes. The mixture was cooled, acidified with aqueous 20% HCl to pH 2 and extracted with Ethyl acetate (3x50 mL). The organic layer was extracted with aqueous 5% Na_2CO_3 (5x50 mL). The alkaline solution was extracted with Et_2O (2x50 mL) and then acidified with aqueous 20% HCl to pH 2. This solution was extracted with Ethyl acetate (4x40 mL) and the recombined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford the intermediate as a pale yellow solid (12.74 g, 85%).

m.p. (Et_2O) 138-140°C
IR (KBr) cm^{-1}: 3450-3000, 1720-1700, 1675, 1650, 1460
PMR ($CDCl_3$) δ:
1.2 (t, 3H, J=6.8), 2.3 (s, 2H), 2.57 (s, 3H), 4.26 (q, 2H, J=6.8), 7.66 (s, 1H), 7.74 (s, 1H), 11.13 (bs, 2H)

By analogous procedure the following compound can be prepared:
E-Ethyl-4-(pyrazol-4-yl)-3-ethoxycarbonyl-3-butenoate

Step -3- **The intermediate 1-acetyl-7-acetyloxy-5-ethoxycarbonyl-3-methyl indazole**

A solution of E-Ethyl-4-[(3-methyl)-pyrazol-4-yl]-3-ethoxycarbonyl-3-butenoate (15.23 g, 64 mmol) in acetic anhydride (320 mL) and sodium acetate (5.25 g, 64 mmol) was refluxed for 5 hours. Then the acetic anhydride was removed under reduced pressure and the residue was diluted with aqueous 15% Na_2CO_3 (100 mL) and extracted with Ethyl acetate (3x50 mL). The recombined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The dark-brown oil was purified by flash chromatography (Et_2O-light petroleum 8.5-1.5) to give the intermediate as a white solid (14.33 g, 70%).

m.p.(Et_2O-light petroleum) 125-126 °C
IR (KBr) cm^{-1}: 1775, 1740, 1720, 1630, 1450
PMR ($CDCl_3$) δ:
1.4 (t, 3H, J=6.8), 2.42 (s, 3H), 2.57 (s, 3H), 2.72 (s, 3H), 4.41 (q, 2H, J=6.8), 7.84 (d, 1H, J=1), 8.20 (d, 1H, J=1)

By analogous procedure the following compound can be prepared:
1-acetyl-7-acetyloxy-5-ethoxycarbonyl-indazole

Step -4- **The intermediate 5-ethoxycarbonyl-7-hydroxy-3-methyl indazole**

A solution of 1-acetyl-7-acetyloxy-5-ethoxycarbonyl-3-methyl indazole (2.88 g, 9 mmol) in dry ethanol (14 mL) and anhydrous potassium carbonate (1.4 g, 10.1 mmol) was refluxed for 18 hours. Then the ethanol was removed under reduced pressure and the residue dissolved in water (20 mL) and the resulting solution extracted with Ethyl acetate (3x20 mL). The recombined organic layers were dried

(Na_2SO_4) and concentrated to afford the crude product that after purification by flash chromatography (EtOAc-light petroleum 1:1) furnished the intermediate as a pale yellow solid (1.86 g, 90%).

m.p. (Et_2O-light petroleum) 230 °C (dec.)
IR (KBr) cm^{-1}: 3370, 1720, 1680, 1640, 1600
PMR ($CDCl_3$) δ:
1.33 (t, 3H, J=6.8), 2.49 (s, 3H), 4.29 (q, 2H, J=6.8), 7.26 (s, 1H), 7.86 (s, 1H), 10.43 (s, 1H), 13.01 (s, 1H)

By analogous procedure the following compound can be prepared:
5-ethoxycarbonyl-7-hydroxy-indazole

Step -5- **The intermediate 7-benzyloxy-5-ethoxycarbonyl-3-methyl indazole**

A solution of 5-ethoxycarbonyl-7-hydroxy-3-methyl indazole (0.9 g, 3.81 mmol) in dry DMF (12.5 mL), under an atmosphere of argon, was treated with anhydrous potassium carbonate (0.7 g, 5.06 mmol) and benzyl bromide (0.51 mL, 4.57 mmol) and stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc-light petroleum 1:2), yielding (1.05 g, 85%) of intermediate as a white solid.

m.p. (Et_2O-light petroleum) 140 °C
IR (KBr) cm^{-1}: 3280, 1700, 1650, 1600
PMR ($CDCl_3$) δ:
1.43 (t, 3H, J=6.8), 2.60 (s, 3H), 4.41 (q, 2H, J=6.8), 5.25 (s, 2H), 7.26-7.52 (m, 6H), 8.09 (s, 1H), 10.22 (bs, 1H)

By analogous procedure the following compound can be prepared:
7-benzyloxy-5-ethoxycarbonyl-indazole

Step -6- **The intermediate 7-benzyloxy-5-ethoxycarbonyl-3-methyl-1-(2-tetrahydropyranyl) indazole**

To a solution of 7-benzyloxy-5-ethoxycarbonyl-3-methyl indazole (0.3 g, 0.92 mmol) in dry CH_2Cl_2, was added 0.2 mL of 2,3-Dihydro-4H-pyran (2.2 mmol) and a catalytic amount of p-Toluenesulfonic acid (10 mg). The mixture was stirred at room temperature for 8 hours. The solution was washed with an aqueous saturated solution of $NaHCO_3$, and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue after purification by flash chromatography afforded the intermediate as a white solid (0.208 g, 98%).

m.p. (Et_2O-light petroleum 1:4) 130-131°C
IR (KBr) cm^{-1}: 1715, 1590
PMR ($CDCl_3$) δ:
1.41 (t, 3H, J=6.8), 1.5-1.8 (m, 4H), 1.85-2.1 (m, 2H), 2.58 (s, 3H), 3.25-3.35 (m, 1H), 3.9-4.01 (m, 1H), 4.40 (q, 2H, J=6.8), 5.25 (s, 2H), 6.1-6.2 (m, 1H), 7.35-7.55 (m, 6H), 8.03 (s, 1H)

By analogous procedure the following compound can be prepared:
7-benzyloxy-5-ethoxycarbonyl-1-(2-tetrahydropyranyl) indazole

Step -7- **The intermediate 7-benzyloxy-3-methyl-1-(2-tetrahydropyranyl)indazol-3-carboxylic acid**

To a solution of 7-benzyloxy-5-ethoxycarbonyl-3-methyl-1-(2-tetrahydropyranyl) indazole (0.51 g, 1.268 mmol) in

THF/MeOH/H_2O in the ratio 4:1:1 (8 mL) was added lithium hydroxide (0.154 g, 3.8 mmol). The mixture was stirred at room temperature for 18 hours. After this time, water was added (20 mL) and the resulting solution was acidified to pH 2 with aqueous 10% HCl. The white precipitate was collected and crystallized (EtOAc-light petroleum) to afford the intermediate as a colorless solid (0.4 g, 86%).

m.p. 230°C (dec.)
IR (KBr) cm^{-1}: 3450-3100, 1685, 1585
PMR ($CDCl_3$) δ:
1.4-1.7 (m, 3H), 1.78-2.08 (m, 3H), 2.56 (s, 3H), 3.3-3.5 (m, 1H), 3.9-4.02 (m, 1H), 5.26 (s, 2H), 6.1-6.2 (m, 1H), 7.40-7.55 (m, 6H), 8.05 (s, 1H), 13.1 (bs, 1H)

By analogous procedure the following compound can be prepared:
7-benzyloxy-1-(2-tetrahydropyranyl)indazol-3-carboxylic acid

Step -8- **The intermediate 7-benzyloxy-5-N-(tert-butyloxycarbonyl)amino-3-methyl-1-(2-tetrahydropyranyl) indazole**

A solution of 7-benzyloxy-3-methyl-1-(2-tetrahydropyranyl) indazol-3-carboxylic acid (0.36 g, 0.94 mmol) in dry tert-Butanol (44 ml) was treated sequentially with diphenylphosphoryl azide (DPPA, 0.23 mL, 1.08 mmol) and Triethylamine (0.15, 1.12 mmol) and the mixture was stirred at reflux for 18 hours. The mixture was cooled and concentrated in vacuo. Flash chromatography (Et_2O-light petroleum 6:4) afforded the intermediate as a white solid (267 mg, 65%).

m.p. (Et_2O-light petroleum) 133 °C
IR (KBr) cm^{-1}: 3400, 1720, 1640, 1600, 1550

PMR ($CDCl_3$) δ:
1.35-1.65 (m, 3H), 1.52 (s, 9H), 1.9-2.05 (m, 3H), 2.46 (s, 3H), 3.3-3.5 (m, 1H), 3.88-4.02 (m, 1H), 5.09 (s, 2H), 6.0-6.15 (m, 1H), 6.8 (s, 1H), 6.9 (s, 1H), 7.2 (s, 1H), 7.35-7.5 (m, 5H)

By analogous procedure the following compound can be prepared:
7-benzyloxy-5-N-(tert-butyloxycarbonyl)amino-1-(2-tetrahydropyranyl) indazole

Step -9- **The intermediate 7-benzyloxy-4-bromo-5-N-(tert-butyloxycarbonyl)amino-3-methyl-1-(2-tetrahydropyranyl) indazole**

A solution of 7-benzyloxy-5-N-(tert-butyloxycarbonyl)amino-3-methyl-1-(2-tetrahydropyranyl) indazole (0.1 g, 0.23 mmol) in 4 mL of dry THF under argon, was cooled to -78° C and treated with a solution of THF (0.8 mL) containing 1.6 μL of concentrated H_2SO_4. After five minutes, N-Bromosuccinimide (50.82 mg, 0.28 mmol) was added and the mixture was stirred at -78°C for 5 hours. The mixture was diluted with Et_2O (20 mL) and washed with saturated aqueous $NaHCO_3$ (2x5 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc-light petroleum 3:7) afforded the intermediate as a white solid (115 mg, 97%).

m.p. (light petroleum) 170°C
IR (KBr) cm^{-1}: 3390, 1730, 1630, 1580, 1540, 1510
PMR ($CDCl_3$) δ:
1.4-1.7 (m, 3H), 1.55 (s, 9H), 1.9-2.1 (m, 3H), 2.76 (s, 3H), 3.2-3.4 (m, 1H), 3.9-4.05 (m, 1H), 5.21 (s, 2H), 6.02-6.1 (m, 1H), 6.99 (s, 1H), 7.39-7.53 (m, 5H), 7.84 (s, 1H)

By analogous procedure the following compound can be prepared:
7-benzyloxy-4-bromo-5-N-(tert-butyloxycarbonyl)amino-1-(2-tetrahydropyranyl) indazole

Step -10- **The intermediate 7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(3-methyl-2-buten-1-yl)]amino-3-methyl-1-(2-tetrahydropyranyl) indazole**

A suspension of Sodium hydride (40 mg, 1.3 mmol, 55-60% in oil) in DMF (4 mL) at room temperature, under argon, was treated with 7-benzyloxy-4-bromo-5-N-(tert-butyloxycarbonyl)amino-3-methyl-1-(2-tetrahydropyranyl) indazole (0.34 g, 0.65 mmol) and the reaction mixture was stirred for 30 minutes. The mixture was cooled at 0°C and commercial 1-bromo-3-methyl-2-butene (0.23 mL, 1.9 mmol) was added slowly. The mixture was allowed to warm to 24°C and was stirred for 3 hours before being poured onto water (15 mL). The mixture was extracted with EtOAc (3x10 mL) and the combined organic extracts were washed with water (10 mL), brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (Et_2O-light petroleum 3:7) afforded the intermediate as a white solid (0.34 g, 90%).

m.p. (Et_2O-light petroleum) 127-128°C
IR (KBr) cm^{-1}: 1680, 1570, 1500
PMR ($CDCl_3$) δ:
1.3 (s, 6H), 1.2-1.6 (m, 3H), 1.48 (s, 9H), 1.8-2.1 (m, H), 2.75 (s, 3H), 3.3-3.55 (m, 1H), 3.85-4.05 (m, 2H), 4.3-4.5 (m, 1H), 5.02 (s, 2H), 5.2-5.25 (m, 1H), 6.05-6.2 (m, 1H), 6.65 (s, 1H), 7.35-7.6 (m, 5H)

By analogous procedure the following compound can be prepared:
7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(3-methyl-2-buten-1-yl)]amino-1-(2-tetrahydropyranyl) indazole

Step -11- **The intermediate 7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(formylmethyl)]amino-3-methyl-1-(2-tetrahydropyranyl) indazole**

A solution of 7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(3-methyl-2-buten-1-yl)]amino-3-methyl-1-(2-tetrahydropyranyl) indazole (90 mg, 0. 15 mmol) in dry CH_2Cl_2-Pyridine (ratio 1:1 40 mL) was cooled to -78°C and was treated with a stream of 3% O_3/O_2 (100 L/h) till solution became light blue. Then the solvent was removed under reduced pressure and the residue was purified by flash chromatography (Et_2O-light petroleum 4:1) to afford the intermediate as a yellow thick oil (70 mg, 83%).

IR (neat) cm^{-1}: 1730-1680, 1580, 1550, 1510

PMR ($CDCl_3$) δ:

1.2-1.55 (m, 3H), 1.35 (s, 9H), 1.8-2.1 (m, 3H), 2.74 (s, 3H), 3.25-3.6 (m, 1H), 3.8-4.05 (m, 2H), 4.5-4.7 (m, 1H), 5.2 (s, 2H), 6.02-6.2 (m, 1H), 6.86-6.89 (m, 1H), 7.39-7.51 (m, 5H), 9.76 (s, 1H)

By analogous procedure the following compound can be prepared:

7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(formylmethyl)]amino-1-(2-tetrahydropyranyl) indazole

Step -12- **The intermediate 7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(3-tetrahydropyranyloxy-2-propen-1-yl)amino-3-methyl-1-(2-tetrahydropyranyl) indazole**

A suspension of triphenyl[(2-tetrahydropyranyloxy)methyl] phosphonium chloride prepared as reported in Tetrahedron 31, 89-92 (1975) (211 mg, 0.51 mmol) in 1.1 mL of dry THF at -78°C was treated dropwise with n-Butyllithium (0.3 mL, 1.6M in hexane, 0.48 mmol). The reaction mixture was stirred at -78°C for 5 minutes and allowed to warm to 24°C

over ten minutes. The mixture was recooled to -78°C and 7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(formylmethyl)]amino-3-methyl-1-(2-tetrahydropyranyl) indazole (100 mg, 0. 17 mmol) in dry THF (0.6 mL) was added dropwise followed by Hexamethylphosphoramide (0.68 mL, 4.1 mmol). The reaction mixture was stirred 20 minutes at -78°C and 12 hours at 24°C before being quenched with the addition of phosphate buffer (35 mL, pH=7.4). The mixture was extracted with EtOAc (3x20 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (Et_2O-light petroleum 3:7) afforded the intermediate (108.2 mg, 93%) as an oil and as a mixture of E-, Z- olefin isomers and diastereoisomers.

IR (neat) cm^{-1}: 1710, 1650, 1570, 1540

PMR ($CDCl_3$) isomeric and diastereomeric mixture δ: 1.2-2.1 (m, 12H), 1.55 (s, 9H), 2.74 (s, 3H) 3.3-3.5 (m, 2H); 3.6-3.75 (m, 1H); 3.9-4.02 (m, 1H), 4.2-4.3 (m, 1H), 4.4-4.6 (m, 1H), 4.75-4.9 (m, 1H), 5.16 (s, 2H), 6.01-6.23 (m, 3H), 6.55-6.78 (m, 1H), 7.4-7.6 (m, 6H)

By analogous procedure the following compound can be prepared:
7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(3-tetrahydropyranyloxy-2-propen-1-yl)amino-1-(2-tetrahydropyranyl) indazole

Step -13- **The intermediate 8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(tetrahydropyranyloxy-methyl)-1-(2-tetraidropyranil)-4,5-dihydro-6*H*-pyrrole[3,2-e] indazole**

A solution of 7-benzyloxy-4-bromo-5-[N-(tert-butyloxycarbonyl)-N-(3-tetrahydropyranyloxy-2-propen-1-yl)amino-3-methyl-1-(2-tetrahydropyranyl) indazole (140 mg, 0.2 mmol) and α,α'-Azo-bisisobutyronitrile (0.64 mg, 0.047 mmol) in

dry benzene (10 mL) at 24 °C under argon was treated with tris(trimethylsilyl)silane (TTMS, 0.178 mL, 0.24 mmol) and the reaction mixture was warmed at reflux for 2 hours. The reaction mixture was cooled and the solvent was removed in vacuo. Flash chromatography (Et_2O-light petroleum 6-4) afforded the intermediate as a colorless oil and as a mixture of diastereoisomers (94.5 mg, 78%).

IR (neat) cm^{-1}: 1715, 1640, 1540

PMR ($CDCl_3$) diastereomeric mixture δ:

1.2-2.1 (m, 12H), 1.58 (s, 9H), 2.62 (s, 3H), 3.2-3.6 (m, 4H), 3.7-4.08 (m, 4H), 4.15-4.3 (m, 1H), 4.5-4.7 (m, 1H), 5.21 (s, 2H), 6.05-6.2 (m, 1H), 7.35-7.55 (m, 5H), 7.8 (s, 1H)

By analogous procedure the following compound can be prepared:

8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(tetrahydropyranyloxy-methyl)-1-(2-tetraidropyranil)-4,5-dihydro-6*H*-pyrrole[3,2-e]indazole

Step -14- **The intermediate (±)-8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(hydroxymethyl)-4,5-dihydro-6*H*-pyrrole[3,2-e]indazole**

A solution of 8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(tetrahydropyranyloxy-methyl)-1-(2-tetraidro-pyranil)-4,5-dihydro-6*H*-pyrazolo[3,2-e]indazole (95 mg, 0.16 mmol) in absolute ethanol (4 mL) was cooled at 0°C and a catalytic amount of p-Toluenesulfonic acid (3 mg) was added and the reaction mixture was stirred at room temperature for 10 hours. Then the mixture was concentrated at reduced pressure and the residue was dissolved in EtOAc (10 mL) and washed with saturated solution of $NaHCO_3$ (5 mL). The organic phase was dried (Na_2SO_4) and concentrated

in vacuo. Flash chromatography (EtOAc-light petroleum 1: 1) afforded the intermediate as a white solid (45 mg, 97%).

m.p. (EtOAc-light petroleum) 120-122°C
IR (KBr) cm^{-1}: 3500-3350, 1710, 1620, 1530
PMR ($CDCl_3$) δ:
1.57 (s, 9H), 2.6 (s, 3H), 3.6-3.9 (m, 3H), 4.0-4.3 (m, 3H), 5.19 (s, 2H), 7.38-7.44 (m, 5H), 7.85 (s, 1H), 11.02 (bs, 1H)

By analogous procedure the following compound can be prepared:
(±)-8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(hydroxymethyl)-4,5-dihydro-6*H*-pyrrole[3,2e]indazole

Step -15- **The intermediate (±)-8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(chloromethyl)-4,5-dihydro-6*H*-pyrrole[3,2-e]indazole**

A solution of (±)-8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(hydroxymethyl)-4,5-dihydro-6*H*-pyrazolo[3,2-e] indazole (486 mg, 1.57 mmol) and Triphenylphosphine (846 mg, 3.14 mmol) in dry CH_2Cl_2 (1.1 mL) at 24°C under argon was treated with freshly distilled Carbon tetrachloride (0.2 mL, 2 mmol), and the reaction mixture was stirred for 20 hours at 24°C. Flash chromatography (Et_2O-light petroleum 4:6) afforded the intermediate (503 mg, 98%) as a white solid.

m.p. (Et_2O-light petroleum) 217-219°C
IR (KBr) cm^{-1}: 3290, 1715, 1610, 1530, 1475
PMR ($CDCl_3$) δ:
1.59 (s, 9H), 2.59 (s, 3H), 3.39 (t, 1H, J=11), 3.65-3.9 (m, 2H), 4.15-4.35 (m, 2H), 5.18 (s, 2H), 7.34-7.44 (m, 5H), 7.85 (s, 1H), 10.5 (bs, 1H)

By analogous procedure the following compound can be prepared:
(±)-8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(chloromethyl)-4,5-dihydro-6H-pyrrole[3,2-e]indazole

Step -16- **The intermediate (±)-6-(*tert*-butyloxycarbonyl)-3-methyl-8-hydroxy-4-(chloromethyl)-4,5-dihydro-6*H*-pyrrole [3,2-e]-1H-indazole [compound (I), no. 27]**

A mixture of (±)-8-benzyloxy-6-(*tert*-butyloxycarbonyl)-3-methyl-4-(chloromethyl)-4,5-dihydro-6*H*-pyrrole[3,2-e] indazole (260 mg, 0.795 mmol), Ammonium formate (240 mg, 4.77 mmol), 10% Pd-C (278 mg) in dry acetone (15 mL) was warmed at reflux for 1h and 30 minutes. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with water (10 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (Et_2O-light petroleum 4:1) afforded the intermediate (169.5 mg, 90%) as a white solid.

m.p. (Et_2O-light petroleum) 230-232°C (dec.)
IR (KBr) cm^{-1}: 3500-3300, 1710, 1620
FAB-MS: m/z 338, (90,$[M+H]^+$). Other fragment ions: 304, 282, 232
PMR (DMSO) δ:
1.57 (s, 9H), 2.59 (s, 3H), 3.42 (t, 1H, J=11), 3.74-3.83 (m, 2H), 4.01-4.15 (m, 2H), 7.61 (s, 1H), 9.2 (bs, 1H), 11.9 (bs, 1H)

By analogous procedure the following compound can be prepared:
(±)-6-(*tert*-butyloxycarbonyl)-8-hydroxy-4-(chloromethyl)-4,5-dihydro-6*H*-pyrrole[3,2-e]-1H-indazole [compound (I), no. 28]

The Title compound [compound (II), no. 3]

100 mg of (±)-6-(*tert*-butyloxycarbonyl)-3-methyl-8-hydroxy-4-(chloromethyl)-4,5-dihydro-6*H*-pyrrole[3,2-e]-1H-indazole (0.42 mmol) was slurried in 1:1:1 Et_3N, H_2O, CH_3CN (10 mL) and the reaction mixture was stirred vigorously for one hour at room temperature. The solvents were partially removed in vacuo and the residue was diluted with brine (15 mL). The solution was extracted three times with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated at reduced pressure. Flash chromatography (EtOAc) afforded the title compound (74.6 mg, 88%) as a pale yellow solid.

m.p. (EtOAc-light petroleum) 214-220°C (dec.)
IR (KBr) cm^{-1}: 3300, 1720, 1620, 1590
FAB-MS: m/z 302, (65,$[M+H]^+$). Other fragment ions: 246, 202
PMR (DMSO) δ:
1.29-1.38 (dd, 1H, J=1, J=4), 1.89 (dd, 1H, J=4, J=8), 1.55 (s, 9H), 2.32 (s, 3H), 3.05-3.15 (m, 1H), 4.15-4.22 (m, 2H), 6.72 (s, 1H), 12.2 (bs, 1H)

By analogous procedure the following compound can be prepared:
(±)-2-(tert-butyloxycarbonyl)-1,2,8,8a-tetrahydrocyclopropa-[c]-pyrazo-[4,3-e]indol-4-one [compound (II), no. 4]

Example 2

(±)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]indol-4-one [compound (II), no. 1]

Step -1- **The intermediate 3-methyl-4-(chloromethyl)-8-hydroxy-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole [compound (I), no. 25]**

The intermediate obtained from the step -16- (20 mg, 0.059 mmol) was treated with anhydrous 3N HCL-EtOAc (2 mL) at 24°C for 1h. The solvent was removed in vacuo to afford the crude intermediate.

By analogous procedure the following compound can be prepared: 4-(chloromethyl)-8-hydroxy-4,5-dihydro-6H-pyrrole [3,2-e]-1H-indazole [compound (I), no. 26]

Step -2- **The Title compound**

Fifteen mg of the compound obtained from the step -1- of Example 2 was treated with 5% aqueous $NaHCO_3$ (2.0 mL) and THF (2.0 mL) at 24°C under N_2, and the two phase mixture was stirred for 8 h (24°C). The reaction mixture was extracted with EtOAc (3x10 mL) and the combined extracts were washed with water (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (AcOEt-CH_2Cl_2 8:2) afforded the title compound (10.12 mg, 85%) as a pale brown solid.

m.p. (EtOAc-light petroleum) >300°C (dec.)
IR (KBr) cm^{-1}: 3300-3200, 1730, 1615, 1580, 1360
PMR (DMSO) δ:
1.25-1.32 (dd, 1H, J=1, J=4.4), 1.95 (dd, 1H, J=4.4, J=8), 2.30 (s, 3H), 3.05-3.15 (m, 1H), 4.10-4.19 (m, 2H), 4.55 (bs, 1H), 7.02 (s, 1H), 12.55 (bs, 1H)

By analogous procedure the following compound can be prepared:
(±)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]indol-4-one [compound (II), no. 2]

Example 3

(±)-2-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]indol-4-one [compound (II), no. 9]

Step -1- **The intermediate 3-methyl-4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl] carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole [compound (I), no. 31]**

A solution of intermediate obtained from the step -16- of Example 1 (100 mg, 0.42 mmol) in 3M HCl-EtOAc (14 mL) at 0°C was stirred for 30 minutes before removing the solvent under vacuum. The resulting crude amine hydrochloride was dissolved in dry DMF (10 mL) and treating sequentially with 5-[(1H-indol-2-ylcarbonyl)amino]-1H-indole-2-carboxylic acid (162.8 mg, 0.5 mmol) (prepared as reported in J.Org.Chem.31, 590-603 (1988)), 1-ethyl-3-(3-dimethylamino-propyl)-carbodiimide hydrochloride (244.8 mg, 1.26 mmol) and the mixture was stirred for 18 hours at room temperature. Water (20 mL) was added to the reaction mixture and the precipitate was filtered obtaining 90 mg of the intermediate.

By analogous procedure the following compounds can be prepared:
4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole; and
4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole.

Step -2- **The Title compound**

Ninety mg of the intermediate obtained from the step -1- of Example 3 was dissolved in 1:1:1 Et_3N, H_2O, CH_3CN (10 mL) and the reaction mixture was stirred vigorously for three hours at room temperature. The solvents were partially removed in vacuo and the residue was diluted with brine (15 mL). The precipitate was collected by filtration and was recrystallized from DMSO/water to afford the title compound (84.2 mg, 50%).

m.p. (DMSO-water) >300°C

IR (KBr) cm^{-1}: 3290, 1650, 1590, 1540
FAB-MS: m/z 503, (30,$[M+H]^+$). Other fragment ions: 302, 202
PMR (DMSO) δ:
1.48 (m, 1H), 2.12 (m, 1H), 2.5 (s, 3H), 3.35 (m, 1H), 4.51 (m, 1H), 4.58 (m, 1H), 6.8 (s, 1H), 6.9-7.8 (m, 8H), 8.23 (s, 1H), 10.21 (bs, 1H), 11.76 (bs, 1H), 11.84 (bs, 1H), 13.5 (bs, 1H)

By analogous procedure and using the opportune starting material [See Tet.Lett., 27, 4103 (1986); W.Wierenga, J.Am.Chem. Soc., 103, No.18, 1981; J.Org.Chem.31, 590-603 (1988)] the following compounds can be prepared:
(±)-2-[[5-[(1H-Benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]indol-4-one [compound (II), no. 11]

m.p. (DMF-water) >300°C
IR (KBr) cm^{-1}: 3275, 1645, 1585, 1540
FAB-MS: m/z 504, (10,$[M+H]^+$). Other fragment ions: 303, 202, 145
PMR (DMSO) δ:
1.46 (m, 1H), 2.15 (m, 1H), 2.47 (s, 3H), 3.3-3.4 (m, 1H), 4.4-4.6 (m, 2H), 6.81 (s, 1H), 7.25-8.13 (m, 8H), 8.22 (s, 1H), 10.5 (bs, 1H), 11.85 (bs, 1H), 13.45 (bs, 1H)

(±)-2-(5-amino-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(±)-2-(5-amino-1H-indol-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(±)-2-(1H-benzofuran-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(±)-2-(1H-benzofuran-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(±)-2-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

(±)-2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(±)-2-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one hydrochloride;
(±)-2-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one hydrochloride;
(±)-2-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one hydrochloride;
(±)-2-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one hydrochloride;
(±)-2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(±)-2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(±)-2-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-yl carbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(+)-2-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(+)-2-[[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
(+)-2-[[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

(+)-2-[[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-yl carbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one; and (+)-2-[[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-yl carbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one.

Example 4

3-methyl-4-(chloromethyl)-6-((tert-butyloxy)carbonyl)-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole [compound (I), no. 29]

One hundred mg (0.42 mmol) of the intermediate obtained from the step -16-, Example 1 is dissolved in the dark in 10 ml of freshly distilled THF. Two equivalents of the phenyl isocyanate and 5 equivalents of triethylamine are added and the reaction mixture stirred for 36 hours under nitrogen at room temperature. The crude product are purified by flash chromatography eluting with acetone-hexane (40/60) to yield 80 mg of the title compound.

By analogous procedure and using the opportune intermediate the following compounds can be obtained:
4-(chloromethyl)-6-((tert-butyloxy)carbonyl)-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl) carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl) carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole; and

4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole.

Example 5

2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one hydrochloride

2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one is dissolved in methanol-water (1:1) and to this solution the stoichiometric amount of 0.1 N HCl is added. After removal of the solvent the title compound is obtained.

Example 6

Intravenous injection 20 mg/ml.

An injectable pharmaceutical preparation can be manufactured by dissolving 20 gr of 2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one hydrochloride in water for injection (1000 ml) and sealing in ampoules of 1-10 ml.

Example 7

Capsules, each dosed at 0.5 g and containing 10 mg of the active substance can be prepared.
Composition for 200 capsules:

2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one	2 g
Lactose	88 g
Corn starch	5 g
Magnesium stearate	5 g

This formulation is encapsulated in two-piece hard gelatin capsules and dosed at 0.5 g for each capsule.

Example 8

Tablets each weighing 0.150 g and containing 10 mg of the active substance, can be manufactured as follows.

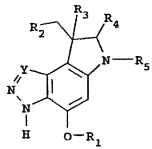
Composition (for 10,000 tablets):

2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one	100 g
Lactose	900 g
Corn starch	450 g
Talc powder	40 g
Magnesium stearate	10 g

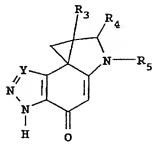
The 2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one, the lactose and half the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm mesh size. Corn starch (10 g) is suspended in warm water (90 ml) and the resulting paste is used to granulate the powder. The granulate is dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and magnesium stearate are added, carefully mixed and processed into tablets.

CLAIMS

1. A compound of formula (I) or (II)



(I)



(II)

wherein

Y is =N- or =CR-, wherein R is hydrogen or C_1-C_4 alkyl;

R_1 is hydrogen; C_1-C_4 alkyl; -COR_6 wherein R_6 is C_1-C_4 alkyl unsubstituted or substituted by phenyl or phenyl in which the phenyl moiety or the phenyl ring is unsubstituted or substituted by 1 to 3 substituents independently chosen from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3; or -$CONH$-R_6 wherein R_6 is as defined above;

R_2 is halogen;

each of R_3 and R_4 independently is hydrogen or C_1-C_4 alkyl;

R_5 is hydrogen or a substituent selected from:

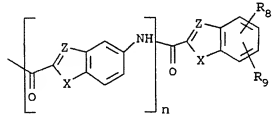
a) COR_7 in which R_7 is i) C_1-C_4 alkoxy or ii) a saturated or unsaturated, straight or branched C_1-C_{18} aliphatic hydrocarbon chain unsubstituted or substituted by one or more substituents independently chosen from hydroxy, C_1-C_4 alkoxy, cyano, -$C(NH)$-NH_2 and -$NR'R''$ in which R' and R'', being the same or different, are hydrogen or C_1-C_4 alkyl, or iii) a saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain ω-substituted by an aryl or

heteroaryl group, which in its turn is unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, hydroxy, C_1-C_4 alkoxy, cyano and -C(NH)-NH_2;

b) a saturated or unsaturated, straight or branched C_1-C_{18} aliphatic hydrocarbon chain unsubstituted or substituted by one or more substituents independently chosen from hydroxy, C_1-C_4 alkoxy, cyano, -C(NH)-NH_2 and -NR'R" in which R' and R", being the same or different, are hydrogen or C_1-C_4 alkyl;

c) a saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain ω-substituted by an aryl or heteroaryl group, which in its turn is unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, hydroxy, C_1-C_4 alkoxy, cyano and -C(NH)-NH_2; and

d) a group of formula (III)



(III)

wherein n is 0, 1 or 2; each of Z group independently is -CH= or -N=; each X group independently is -O-, -S-, -NR-, wherein R is as defined above; and each of R_8 and R_9 independently is hydrogen, halogen, hydroxy, C_1-C_4 alkoxy, cyano, -C(NH)-NH_2 or -NR'R" wherein R' and R" are as defined above; and pharmaceutically acceptable salts thereof.

2. A compound of formula (I) or (II), according to claim 1, wherein:

R_1 is hydrogen; $-COR_6$; or $-CONH-R_6$ wherein R_6 is as defined in claim 1;

R_3 and R_4 are hydrogen;

R_5 is a group of formula (III) as defined in claim 1;

R_2 and Y are as defined in claim 1; and the pharmaceutically acceptable salts thereof.

3. A compound of formula (I) or (II), according to claim 1, wherein:

Y is =CH- or $=C(CH_3)-$;

R_1 is hydrogen or $-CONHR_6$ wherein R_6 is as defined in claim 1;

R2 is as defined in claim 1;

R3 and R4 are hydrogen;

R_5 is a group of formula (III) as defined in claim 1 wherein Z is CH and X is independently O, NH or NCH_3; R_8 is hydrogen and R_9 is as defined in claim 1; and the pharmaceutically acceptable salts thereof.

4. A compound selected from the group consisting of:
7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-(tert-butyloxycarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-(tert-butyloxycarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-(5-amino-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-(5-amino-1H-indol-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;

2-(1H-benzofuran-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-(1H-benzofuran-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclo-propa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclo-propa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-

1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
2-[[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]-pyrazo-[4,3-e]-indol-4-one;
3-methyl-4-(chloromethyl)-8-hydroxy-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;
4-(chloromethyl)-8-hydroxy-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-8-hydroxy-6-((tert-butyloxy)carbonyl)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;
4-(chloromethyl)-8-hydroxy-6-((tert-butyloxy)carbonyl)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-((tert-butyloxy)carbonyl)-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;
4-(chloromethyl)-6-((tert-butyloxy)carbonyl)-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl) carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(1H-benzofuran-2-yl carbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl) carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl] carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

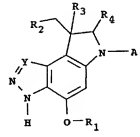
4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;

3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-

2-yl]carbonyl]-8-((N-phenyl) carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy)-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
3-methyl-4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl]carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole;
4-(chloromethyl)-6-[[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-yl] carbonyl]-8-((N-phenyl)carbamoyloxy-4,5-dihydro-6H-pyrrole-[3,2-e]-1H-indazole; either as single isomers or a mixture thereof, or a pharmaceutically acceptable salt thereof.

5. A process for the preparation of a compound of formula (I) or (II), or a pharmaceutically acceptable salt thereof, the process comprising:

a) removing the protecting group in a compound of formula (IV)



(IV)

wherein A is an amino protecting group, R_1 is hydrogen and Y, R_2, R_3, R_4, are as defined in claim 1, under acidic conditions, thus obtaining a compound of formula (I) in which R_1 and R_5 are hydrogen; or

b) reacting a compound of formula (I), wherein R_5 is hydrogen and Y, R_1, R_2, R_3 and R_4 are as defined in claim 1, with a compound of formula (V)

$$R'_5\text{-}W \qquad (V)$$

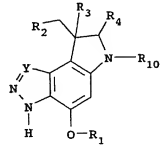
wherein R'_5 is as R_5 defined in claim 1 under a) or d) and W is OH or a good leaving group, thus obtaining a compound of formula (I) wherein R_5 is as defined in claim 1 under a) or d), respectively; or

c) reacting a compound of formula (I), wherein R_5 is hydrogen and Y, R_1, R_2, R_3 and R_4 are as defined in claim 1, with a compound of formula (VI)

$$R''_5\text{-}W' \qquad (VI)$$

wherein R''_5 is as R_5 defined in claim 1 under b) or c) and W' is halogen, thus obtaining a compound of formula (I), wherein R_5 is as defined in claim 1 under b) or c), respectively; or

d) reacting a compound of formula (VII)



(VII)

wherein R_1 is hydrogen, R_{10} is either an amino protecting group or as R_5 as defined in claim 1

under a) to d) and Y, R_2, R_3 and R_4 are as defined in claim 1, with a compound of formula (VIII)

$$W'\text{-}C_1\text{-}C_4 \text{ alkyl} \qquad \text{(VIII)}$$

wherein W' is halogen, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I), wherein R_1 is C_1-C_4 alkyl; or

e) reacting a compound of formula (VII) as defined above with a compound of formula (IX)

$$W\text{-}COR_6 \qquad \text{(IX)}$$

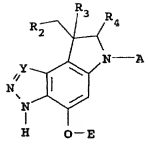
wherein W is as defined above and R_6 is as defined in claim 1, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I) wherein R_1 is $-COR_6$; or

f) reacting a compound of formula (VII) as defined above with a compound of formula (X)

$$R_6\text{-}N{=}CO \qquad \text{(X)}$$

wherein R_6 is as defined in claim 1, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I) wherein R_1 is $-CONR_6$; or

g) removing the amino and hydroxy protecting groups in a compound of formula (XI)



(XI)

wherein E is a hydroxy protecting group, A is an amino protecting group and Y, R_2, R_3 and R_4 are as defined in claim 1, thus obtaining a compound of formula (I) wherein R_1 and R_5 are hydrogen; or

h) removing the hydroxy protecting group in a compound of formula (XI) wherein A, being as defined above is -COO-tert-butyl, is as defined above and E, Y, R_3 and R_4 are as defined in claim 1, thus obtaining a compound of formula (I) wherein R_1 is hydrogen and R_5, being a COR_7 group as defined in claim 1, is -COO-tert-butyl; or

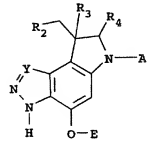
i) reacting a compound of formula (I), in which R_1 is hydrogen and Y, R_2, R_3, R_4 and R_5 are as defined in claim 1, with a basic agent, thus obtaining a compound of formula (II);

and if desired, converting a compound of the invention into another compound of the invention, and/or, if desired converting a compound of the invention into a salt thereof, and/or, if desired converting a salt of a compound of the invention into a free compound, and/or, if desired, separating a mixture of isomers of a compound of the invention into the single isomers.

6. A pharmaceutical composition containing a suitable carrier and/or diluent and, as an active principle, a compound of formula (I) or (II), according to claim 1, or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I) or (II), or a pharmaceutically acceptable salt thereof, for use as an anti-tumor agent.

8. A compound of formula (XI)



(XI)

wherein E is a hydroxy protecting group; A is an amino protecting group and Y, R_2, R_3 and R_4 are as defined in claim 1.

The Patent Office

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Application No:	GB 9510169.7	**Examiner:**	Roy Honeywood
Claims searched:	1-8	**Date of search:**	16 July 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C2C (CTY CKS CLL CWC CBC CKH CKR)

Int Cl (Ed.6): C07D

Other: ONLINE: CAS

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	None	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.